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SENT VIA UNITED PARCEL SERVICE

Dockets Management Branch
Food and Drug Administration
HFA No. 305, Room No. 1061
5630 Fishers Lane
Rockville, MD 20852

AUG 26 1999

Dear Madam or Sir:

Re: Docket Number 99N-0193

Reference is made to the FDA Proposed Rule, Code of Federal Regulations 3 14.70, which was published in the Federal Register on June 28, 1999.

Astra Pharmaceuticals and Zeneca Pharmaceuticals has reviewed this draft proposed rule; our comments are attached.

Please do not hesitate to contact me should you require &.&cation on any of the above comments.

Sincerely,

Robert Castor
Assistant Director
Chemistry, Manufacturing and Controls Group
Regulatory Affairs Department
(302) 886-2594
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RC/CSF/jr
Enclosure

99N-0193

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Comments on Proposed 21 CFR 314.70

Astra Pharmaceuticals and Zeneca Pharmaceuticals

General Comments

The introduction of the Federal Register Notice accompanying the Proposed Rule, clearly states that 21 CFR 3 14.70 has been amended by the Food and Drug Administration Modernization Act (FDAMA). Many of the suggested requirements proposed here are counter to the spirit and literal meaning of FDAMA, which was enacted to provide regulatory relief without compromising quality, safety, or efficacy of drugs.

Section 116 of FDAMA clearly states the situations in which a sponsor will make a change that may have "major" implications for safety or efficacy of the drug substance or product in question. Major changes are clearly stated in the Act as formulation, specification, or bioequivalence changes. These types of post-approval changes require prior approval (PA) from the Agency before the change is implemented. Many of our specific comments are linked to the issue that the Agency has proposed PA supplements for changes that are clearly outside of the 3 major change categories described in FDAMA and/or justification of a proposed change being filed as PA is not provided.

The degree to which a change will likely affect product identity, strength, quality, purity, and potency should be consistently linked to the chance that the proposed change will adversely affect the drug substance or product. The guidance is inconsistent with FDAMA in this area, since many changes that are considered "major", are really "moderate" or "minor" changes and some "moderate" changes are of minor consequence. A few "minor" changes do not require regulatory filings at all.

In addition to discrepancies with FDAMA, this Guidance also is counter to previously published Agency guidances such as SUPAC. If the Agency has already determined that providing regulatory relief via SUPACs and other guidances is acceptable practice, then we respectfully question the reasoning behind changing these same policies back to a more burdensome state.

New regulations pertaining to natural products that appear in the CFR are burdensome to Industry and should be deleted.

Specific Comments on the Proposed Regulations

Regulation	Comments
3 14.70(a)(6)	"..annual report shall include in the cover letter.. ."
	We believe that cover letters are not appropriate for Annual Reports (AR). Form FDA 2252 is used as the cover letter and table of contents.
3 14.70(b) (2) (ii), (iii), (iv), and (vi)	The proposed regulation references changes that "may relate to the safety or effectiveness.. ." Please clarify if this means that a prior approval supplement would be required even if it is demonstrated that the change has no significant adverse affect.
	In addition, part (iii) lists changes to sterile products as PA supplements, which is too restrictive, and already in contradiction to the draft guidance which allows for a less burdensome method for selected changes to sterile products. Some of the changes discussed here are GMP concerns. We believe that only fundamental changes to sterile processing require PA.
314.70(b)(iv)	This does not agree with recommendations in BACPAC I and is too restrictive.
314.70(b)(2)(vii) (A)(B)(C)	New regulations governing natural products are restrictive and should be deleted.
314.70(d)(2) (i)	This section says that any "change made to comply with an official compendium, *that* is consistent *with FDA requirements.. ."* is an AR tiling. This statement implies that there may be separate and/or different requirements to fulfill USP and FDA criteria. This situation is burdensome since Industry has always assumed that USP requirements were consistent with FDA thinking. Further, Section 501 (b) of the Federal Food, Drug and Cosmetic Act states that if drug product meets compendia1 requirements, it is considered unadulterated. Please clarify this statement.
	Specifically, if the regulation is intended to require prior approval supplements for deleting or widening a specification due to a change in USP, we disagree with this proposal. Please clarify this issue.
	We recommend that any change made to comply with an official compendium should be annual reportable.

Specific Comments on Draft Guidance for Industry: "Changes to an Approved NDA or ANDA"

Regulation	Comments
314.70(d)(2)(ii)	We believe that changes in formulation, regardless of the intended purpose of the ingredient, are more appropriately addressed in terms of percent change allowed at each level as delineated in the SUPAC Guidances.
314.70 (d)(2)(vi)	The extension of an expiration dating period based upon full shelf-life data on full production batches is restrictive. FDAMA provides for the use of pilot scale batches to demonstrate safety and effectiveness of the drug; ICH also approves of using pilot scale batches for approval of expiry dating. Additionally, the Draft Guidance, "Stability Testing of Drug Substances and Drug Products" state that pilot scale batches may be used for tentative approval and extension of expiry dating. We believe that use of pilot scale batches to confirm an expiry date is scientifically justifiable and that this should be apparent in the regulation and in related guidances.
314.70(d)(3)(iii)	Please clarify the intent of requiring references to "validation protocols and/or SOPS". If the intention is to submit validation protocols and SOPs in the AR, then this is a more restrictive requirement and is inconsistent with, "Guidelines on the Content and Format of the CMC Section of an Annual Report". Validation protocols and SOPs are GMP issues and would more appropriately be the subject of a pre-approval inspection (PAD, not an AR.

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